Section II (Remarks)

A. Summary of Amendment to the Claims

By the present Amendment, Claim 5 has been amended to depend from Claims 1-3 rather than Claims 1-4, and new Claim 52 has been added, including essentially the same language as Claim 5, but being dependent on Claim 4. Claim 49 has been amended to incorporate the limitations of Claims 50 and 51, which claims have been cancelled. Further, Claims 6-29 and 40-43 were cancelled, and Claims 30-39 were previously cancelled.

New Claims 53-60 have been added, which are directed to compositions comprising unit dosage forms of rifalazil with low dosage ranges in each unit dose, plus instructions for administration in a daily dosing schedule. Support for these claims can be found in the specification as shown below:

> [0008] The invention also features a method of treating a bacterial infection by administering a low-dosage rifalazil regimen. The low-dosage regimen includes the step of administering to a patient between 0.01 and 10 mg of rifalazil over a period of four to fourteen days. Desirably, between 0.1 and 10, 0.01 and 8, 0.01 and 6, 0.05 and 8, 0.05 and 6, 0.1 and 5, 0.1 and 4, 0.1 and 3, 0.1 and 2.6, or 0.2 and 2.0 mg of rifalazil is administered over a period of five to ten days, or over a period of seven days.
>
> [0009] The invention also features a method of treating a bacterial infection by administering rifalazil daily. This method includes the step of administering to a patient between 0.01 and 5 mg of rifalazil daily over a period of at least 2 days. Desirably, between 0.1 and 5, 0.1 and 4, 0.1 and 3, 0.1 and 2.6, 0.1 and 1.8, 0.01 and 4, 0.05 and 4.6, 0.05 and 4, or 0.1 and 1.6 mg of rifalazil is administered daily for a period of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60, or 90 days.

The newly added claims, which include two multiple dependent claims, add up to 19 total claims. Claims 6-29 and 40-43 have been cancelled, and, accordingly, the number of newly added claims does not exceed the number of previously paid for claims that are now cancelled.

The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

B. Rejection Under the Judicially-Created Doctrine of Obviousness-Type Double Patenting

Claims 1-5 and 49-51 were rejected under the judicially-created doctrine of obviousness-type double patenting over Claims 43-45 of co-pending U.S.S.N. 10/948,608. A terminal disclaimer is attached, thus mooting the rejection.

Claims 1-5 were rejected under the judicially-created doctrine of obviousness-type double patenting over Claim 4 of U.S. Patent No. 7,220,738 and Claim 4 of U.S. Patent No. 4 of U.S. Patent No. 7,271,165.

U.S. Patent No. 7,271,165 is directed to rifamycin analogs, with a formula that does not include rifalazil. The claims in the instant application are limited to rifalazil. Claim 4 of the '165 patent is directed to:

> 4. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

Thus, there is no mention of rifalazil, or the low doses of rifalazil present in the instantly claimed composition claims. Rifamycin analogs other than rifalazil do not render obvious rifalazil-containing compositions, at least for the reason that the rifamycin analogs were developed as purported improvements over rifalazil. To say that a generic formulation of a non-rifalazil rifamycin analog renders obvious a specific rifalazil composition overlooks every aspect of the claimed subject matter – the compound and the way it is administered. Applicants respectfully suggest that Claim 4 of the '165 does not render obvious the claims as currently pending, and the rejection should be withdrawn.

U.S. Patent No. 7,220,738 is directed to other rifamycin analogs, which, like the '165 patent, do not include rifalazil. Claim 4 of the '738 patent is worded identically to Claim 4 of the '165 patent, though it relates to rifamycin analogs which are patentably distinct from the rifamycin analogs in the '165 patent.

For the same reasons, the instantly claimed subject matter is not obvious over the subject matter of the '738 patent.

C. Rejection Under 35 U.S.C. § 103 (a)

Claims 1-3, 5 and 49-51 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,316,433 to Rose in view of Remington's Pharmaceutical Sciences (hereafter "Remington"). Specifically, the Office Action states that Rose teaches pharmaceutical compositions of rifalazil in a unit dosage amount from 1mg to 5mg for oral administration and Remington provides motivation to prepare the pharmaceutical formulation for oral administration as recited by claims 49-51. Applicants disagree and traverse the rejection for the following reasons.

Claims 1-3, 5, and 49-51 are Non-Obvious over Rose in view of Remington

Specifically, the Office Action states that Rose discloses a drug unit in tablet form having 1mg of Rifalazil, which the Office contends is within the stated ranges of claims 1-3 and administered in the same form as listed in claim 5. Applicant disagrees, and traverses the rejection for the following reasons.

Claims 1-4 recite pharmaceutical compositions of rifalazil at low concentrations, with claim 1 reciting a range of from 0.1mg to 5mg, and claims 2-4 reciting ranges of 0.1-3mg, 0.1mg-1.0mg, and 0.2mg to 0.4mg, respectively. By present amendment, claims 2-4 are now independent claims.

In column 34, at line 21, claim 11 of Rose recites the administration of rifalazil once or twice a week "in dose from 1 mg to about 50mg orally" (Rose, claim 11). Rose, however, does not teach administration of a 1 mg dose of rifalazil in any of the clinical trials that are disclosed. ("...a single 300mg does of rifalazil..." col. 11, ll. 25-26; "...administration in dosages 0, 5, and 25 mg. a day..." col. 11, ln. 40; "weekly doses of placebo or rifalazil (25mg or 50mg)..." col. 11, ln 55; ..."receiving doses of 30mg, 100mg, and 300mg of rifalazil." col. 12, ln. 23; "administration of rifalazil as single doses (300mg, 100mg, 30mg), daily doses (25mg, 5mg) administered for 14 days, and weekly doses (50mg, 25mg) administered for 4 weeks." col. 22, ll. 55-59; "For clinical studies described above, rifalazil capsules have been prepared at several strengths; 5mg, 25mg, 50mg and 100mg." col. 32, ll. 8-11)

In fact, Rose does not teach administering rifalazil at 1mg orally in tablet or capsule form anywhere in the specification. It is also correct to state that Rose used rifalazil in Tuberculosis only, co-administered with INH, and the 10 mg dosage did not work well in that trial as compared to the 25 mg (plus INH) arm. Accordingly, one of skill in the art would have no

expectation of success by going to a dosage lower than 10 mg, and certainly would not expect that even lower doses would be effective, even though a broader range was generically taught, since there is no teaching of any type of disorder for which such lower dosage range is effective.

While Applicants claims are composition claims, Applicants specification teaches that such low doses are effective when administered on consecutive days. As discussed in more detail below, Rose teaches away from daily administration. One of skill in the art would not be motivated to try lower dosages than those which Rose teaches were not even effective, particularly when the only way the dosages would be effective is if they were administered in a daily fashion (which in any event is only taught by the instant application) and Rose teaches away from daily administration.

Since Rose does not teach the oral administration in tablet or capsule form of a unit dose of rifalazil at 1mg, Rose does not anticipate the administration of rifalazil at the concentration ranges recited by claims 1-5. Accordingly, Applicants respectfully request that this rejection be withdrawn if applied to the amended claims.

Claim 52 is similar to Claim 5, except that it depends from Claim 4, so the same arguments apply, and, additionally, Claim 4 was not rejected, so Claim 52 should similarly not be rejected.

Arguments Related to Claim 49

Claim 49 has been amended to include the limitations of Claims 50 and 51, which claims have been cancelled. Thus, not only does Claim 49 teach the use of a loading dose, the loading dose is followed by a lower dose within the same dosage ranges of Claim 1. Thus, for the same reasons discussed above, Claim 49 is non-obvious.

Accordingly, Applicants respectfully request that the obviousness rejections be withdrawn if applied to the amended claims.

New Claims 53-60 are Non-Obvious over Rose in view of Remington

New Claims 53-60 are directed to compositions comprising unit dosage forms providing for low dose rifalazil, and instructions for daily administration for a given period of days. These claims are non-obvious over Rose in view of Remington.

First and foremost, the Abstract of Rose teaches that the invention is directed to:

> A method for treatment of bacterial infections with rifalazil administered once-weekly or twice-weekly. A method for treatment of tuberculosis caused by Mycobacterium tuberculosis, infections caused by Mycobacterium avium complex, infections caused by Chlamydia pneumoniae and infections caused by Helicobacter pylori by administering to a patient suffering from the bacterial infection 1-100 mg of rifalazil once or twice a week. In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of rifalazil.

Rose's Field of the Invention states:

> In this dose regimen, the treatment is fast, efficacious and eliminates undesirable secondary symptoms observed with daily doses of 1-50 mg of rifalazil.

Rose's Background of the Invention states:

> Newly discovered once-week or twice-week regimen has the same efficacy as daily administration and yet eliminates or significantly decreases the adverse reactions.... Previously, rifalazil has been administered on daily basis and because of the severe secondary adverse reactions, was discontinued as a drug for treatment of tuberculosis and other infection. Newly discovered once-week or twice-week regimen has the same efficacy as daily administration and yet eliminates or significantly decreases the adverse reactions.

(emphasis added)

Rose's summary of the invention states:

> One aspect of the current invention is a method for treatment of bacterial infections with once or twice-week administration of rifalazil.
> Another aspect of the current invention is a method for treatment of tuberculosis with once or twice-week: administration of rifalazil.
> Still another aspect of the current invention is a method for treatment of Mycobacterium avium complex infections with once or twice-week administration of rifalazil.

> Still another aspect of the current invention is a method for treatment of Chlamydia pneumoniae infections with once or twice-week administration of rifalazil.
> Yet another aspect of the current invention is a method for treatment of Helicobacter pylori infections with once or twice-week administration of rifalazil.

Rose's Detailed Description states:

> Although rifalazil was found to be effective against mycobacterium species, it has never been used as a therapeutic agent for treatment of mycobacterial diseases because at the daily dose regimen which was thought to be necessary to its efficacious antibacterial activity, rifalazil caused severe adverse reactions and secondary symptoms.

Remington is a generic teaching, whereas Rose specifically points to problems associated with daily dosing of rifalazil. Given Rose's extremely negative statements throughout the specification regarding daily dosing of rifalazil, it is clear that Rose teaches away from daily dosing. Teaching away is the antithesis of obviousness, and nothing in Remington can overcome that teaching away.

New Claims 53-60 are directed to compositions in unit dosage form comprising rifalazil in a dosage of between 0.1 and 5 mg, 0.1 and 3 mg, or 0.1 and 1 mg/day, with instructions for dosing on a daily basis for a period of time of four to fourteen days, four to ten days, daily for at least a period of two days, daily for at least a period of five days, daily for at least a period of ten days, and daily for at least a period of thirty days.

Rose purportedly solved the problems associated with daily dosing by going to a weekly dosing formulation. The present invention solves the problems associated with daily dosing by going to a lower dosage that does not provide the same side effect profile, while still providing efficacy.

Accordingly, these claims are non-obvious over Rose, alone or in combination with Remington.

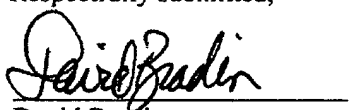
D. Fees Payable for Added Claims, a Terminal Disclaimer, and for a Two Month Extension of Time

Payment of the $70.00 fee to file a terminal disclaimer, plus the $245.00 for a the applicable two month extension of time, results in a total fee of $315.00 that is authorized in the enclosed Credit Card Payment Form PTO-2038.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 1-5, 49, and 52-60 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,



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Enclosures:
Credit Card Form PTO-2038 [1 pg.]
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